Author's response to reviews

Title: Clinical characteristics and prognostic factors of bone lymphomas: focus on the clinical significance of multifocal bone involvement by primary bone large B-cell lymphomas

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Version: 3 Date: 17 November 2014

Author's response to reviews: see over
Dear Editor-in-Chief and reviewers,

We really appreciate for the time and efforts you spent reviewing our manuscript. Your professional comments are valuable in helping us to improve the quality of manuscript. We have seriously addressed your critiques by point-to-point responses, and made substantial revisions according to your suggestions in the revised manuscript.

Again, thank you very much for all your helps to make the manuscript publishable. We are looking forward to hearing a positive feedback soon.

Best regards

Ling Zhang, MD

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Response to Reviewers:

Reviewer 1
Reviewer: Girish Venkataraman
Reviewer's report:

Major

The study details cases of primary bone lymphoma including a disparate group of low-grade B-cells to aggressive large B-cell as well as few T-cell lymphomas and even classical Hodgkin lymphoma and has looked at outcome in a heterogeneous group of entities with very different treatment regimens and outcome otherwise. Ideally, it would be more informative to only examine the DLBCL and BCLU group excluding all the other cHL, LGBCL and T-cell entities

Response:
According to your suggestion, only patients with DLBCL were analyzed for patient characteristics and prognostic factor analyses in the present manuscript.

Treatment regimens, IPI, LDH information need to be included.

Response:
Treatment regimens and LDH information has been added according to your valuable suggestion. (Treatment: Pg 10 and table 4; Pg 15, lines 15-17) (LDH: table 2 and 5 and Pg 11, lines 20-22) Given that the prognostic significance of IPI had been extensively discussed in our previous study in BJH (Wu H, et al. British journal of haematology 2014, 166(1):60-68.), it will not be discussed in our current study to avoid redundant information.

Discussion of your recent paper in BJH and how this information complements that paper is necessary. Please delete redundant elements already published in that paper.

Response:
Our prior study published in BJH (Wu H, et al. British journal of haematology 2014, 166(1):60-68.) had explored the potential prognostic factors using the new 2013 WHO classification in 70 PBL cases and revealed that soft tissue extension and IPI score were the most important unfavorable prognostic factors for both PFS and OS in PB-DLBCL. However, there is still no universal consensus on whether patients who present with multifocal bone lesions should be diagnosed as PBL or SBL. Moreover, it is almost impossible to distinguish multifocal bone involvement of PBL (mPBL) from SBL clinically and radiologically in patients with advanced-stage disease (particularly in those PBL with regional lymph node and/or adjacent soft tissue involvement). The clinical and prognostic significance of multifocality in PBL was not well discussed in our previous study, which had not yet compared with conventional SBL. Given these considerations, we expanded our sample size from 70 to 127 in the current study, which included a series of 81PBL patients and 46 SBL patients. The 127 patients with bone lymphoma were further subcategorized into uPBL, mPBL, and SBL. We compared patient characteristics, treatments and outcome among PBL and SBL groups, aiming to further explore the clinical and prognostic
significance of multifocality in PBL and examine the current definition of PBL. Because of the rarity of the other cell types, only patients with DLBCL of bone, primary or secondary, are analyzed for prognostic factors. Our current study confirmed that mPB-DLBCL had similar patient characteristics, treatments and poor outcome with SBL, and multifocality was an independent prognostic factor for PB-DLBCL. Our results might contribute to the definition of PBL, and so-called “mPBL” should be better classified as SBL, rather than a conventional PBL with unifocal bone disease. Our results indicated that it might be unnecessary to distinguish mPBL from SBL, clinically. In addition, we also explored the prognostic significance of CD10, bcl-6, bcl-2 and mum-1 expression in PB-DLBCL by using all available data.

Our BJH study has been cited and discussed by the current manuscript. (Pg 5, lines 4-7; Pg 7, lines 13-14)

Of note, the information related to soft tissue extension and IPI, which has been extensively discussed in our previous study, will not be further discussed in the current study in revised version in order to avoid redundant information.

Minor

*Was the HIV status of these patients known?*

**Response:**
Yes. Among the 127 bone lymphoma patients, only two PBL cases were HIV positive, including one DLBCL and one large B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and Bukkit lymphoma (BLUI). The piece of information has been added into the Results section. (Pg 8, line 22; Pg 9, lines 1-3)

*Typos such as SLB, male female ratio with slightly male predominance of “1:5” etc.*

**Response:**
Thank you. The typographic errors have been corrected.

*LDH levels need inclusion*

**Response:**
The level of LDH has been included. (*LDH: table 2 and 5 and Pg 11, lines 20-22*)

*Discretionary*

*Mum1 was not done in most cases but then many were BCL-2+. It would be good to know the proliferation and maybe the MYC IHC status is available since majority of cases classified as PBL are DLBCLs. It would better for the table to be depicted as a bar graph or at the least depicted as likely GC-origin vs. non-GC origin*
and give numbers of BCL2+ cases within these two subgroups.

Response:
The retrospective study comes across the data collected between 1998 and 2003. Many cases have had performed limited immunophenotyping (flow cytometry and/or IHCs) at diagnosis and left PBL-DLBCL no further subclassification into GCB or non-GCB subtype. According to your critique, we have tried our best to retrieve the original specimens, unfortunately, a large subset of the cases with incomplete IHC study was originally diagnosed by an outside facility. Therefore, it is very difficult for us to ask for the archival paraffin blocks from these facilities for additional IHC or FISH study.

As learned, it might not be necessary to further subclassification of GCB or non-GCB type PBL-DLBCL because of their limited clinical importance in the setting. *(Reference: Bhagavathi S et al. Am J Surg Pathol 2009(33):10,1463-69.)*

We have mentioned in the Discussion section that “However, incomplete IHC data of MUM-1 in our study precluded an accurate subclassification of our PB-DLBCL cases into GCB or non-GCB subgroups. Despite so, 26 of 43 patients were able to be classified with PB-DLBCL in our series according to CD10-positivity, which meant that at least 60.5% of these patients were of GCB phenotype”.
Additional material submitted by the reviewers

Referee 1:

Reviewer #1:

This is a fairly large series of PBL cases of various histologic subtypes compared with systemic lymphoma with bone involvement. The authors indicate that unifocal PBL has a good outcome and that T-cell histology is associated with worse outcome. Conceptual issues. The study details cases of primary bone lymphoma including a disparate group of low-grade B cells to aggressive large B-cell as well as few T-cell lymphomas and even classical Hodgkin lymphoma and has looked at outcome in a heterogeneous group of entities with very different treatment regimens and outcome otherwise. Ideally, it would be more informative to only examine the DLBCL and BCLU group excluding all the other cHL, LGBCL and T-cell entities. The survival analysis as done is not a fair comparison and very hard to infer. Also, unifocal PBL-DLBCL and unifocal cHL in the bone is not going to be treated the same way. So it is hard to generalize any treatment decisions based on primary bone location. For e.g. a good comparison group for bone T-cell lymphoma would be systemic T-cell lymphoma with or without bone involvement not all bone lymphomas. Data on LDH is also relevant but not included. Treatment regimens for the various diseases detailed in the study are not discussed. Data on IPI is not included although your group has very recently published another paper in BJH describing (presumably) the same cases comparing uPBL with multifocal PBL.[1] There is no discussion or reference to this work in your current manuscript. Please also discuss the prognostic factors such as age, IPI as it related to outcome in DLBCL subgroup as discussed by the Ramadan paper from the BCCA group.[2] Also, the extensive discussion of the different bone sites involved does not seem to have any prognostic relevance.

Response:

According to your professional suggestion, we only analyzed the patients with DLBCL for clinical characteristics and prognostic factors in the current manuscript. Per suggestion, treatment regimens and LDH information has been included. The contents related to the prognostic significance of IPI and age are minimized in our current study to avoid redundant elements.

Of note, our manuscript was submitted to BMC Cancer on 1 April 2014, while our BJH paper was first published online on 27 March 2014 and formally published in Jul 2014. The prior data published in BJH has been cited in the currently revised manuscript. (Pg 5, lines 4-7; Pg 7, lines 13-14)

In addition, according to your suggestion, the sentences “Appendicular bone (including long and short bones of limbs, scapula, and pelvic bones) involvement was more commonly shown than axial bone involvement (including vertebrae, ribs, sternum, clavicle, bones of the skull and face, and mandible) in the uPBL group,
whereas cases with both axial and appendicular bone involvement were common in the other groups” have been deleted in the revised manuscript.

Other comments:
Page 1, line 5-6 doesn't make sense to me: Whether patients with multifocal bone involvement should be considered as having "PBL from SBL" still remain controversial.
- Do you mean "SBL from PBL"?
Response:
To clarify the statement, this sentence has been revised to "Whether lymphoma with multifocal bone involvement should be considered as stage IV PBL or SBL still remain controversial throughout the literature ". (Pg 1, lines 4-5)

Page 5, line 1: ".. information was there in included regarding"
- This must be a typo
Response:
Thank you for your pin pointing the error. It has been corrected to "However, limited information was available on the prognostic role of multifocality in PBL". (Pg 5, line 8)

Page 6: There seems a lack of uniformity regarding assessment of lymph nodes. All lymph nodes > 1.5cm was regarded as malignant disease. Was this by PET? CT? How many cases were actually biopsy-proven lymph node involvement?
Response:
According to AJCC Cancer Staging Manual (Reference: Hodgkin and Non-Hodgkin Lymphomas. In: Edge SB, Byrd DR, Compton CC, et al., eds.: AJCC Cancer Staging Manual. 7th ed. Springer, 2010, pp 6.), lymph node involvement is demonstrated by (a) clinical or imaging enlargement of node when alternative pathology may reasonably be ruled out. Nodes larger than 1.5 cm are considered abnormal. In our series, lymph nodes were assessed by the Positron Emission Tomography (PET) scan. The majority were followed by a CT guided biopsy. The piece of information has been added. (Pg 6, line 9-11)

Page 8: Line 18. Hodgkin lymphoma involving bone is more common than DLBCL. FL is understandable but stage IV cHL is generally more common in HIV patients. Was the HIV status of these patients known?
Response:
What we meant was that compared with PBL groups, SBL group had a higher proportion of cHL and thus a relatively lower proportion of DLBCL. Actually, according to the literature and our own experience, primary bone cHL is extremely rare. However, it is no doubt that DLBCL was also more common than cHL in SBL groups. The only cHL in our PBL groups were staged as IIE. As for HIV status,
among the 127 bone lymphoma patients, only two PBL cases were HIV positive, including one DLBCL and one large B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and Bukkit lymphoma (BLUI). It has been added into the Results section. (Pg 8, line 22; Pg 9, lines 1-3)

Page 10: It is unclear to me whether gender was included in the multivariate analysis since there was a male predominance in the 4 groups.

Response:
In our study, a Cox proportional-hazards regression model was used to perform multivariate survival analysis using a forward variable selection procedure. Only the variables with significant values (P≤0.05) in univariate analysis were included in the multivariate analysis. Gender had no significant values (P>0.05) in univariate analysis, and thus it was not included in the multivariate analysis. We have added the information in the Methods section. (Pg 8, lines 8-9)

Page 14: In the discussion, there is a cursory mention of treatment for unifocal bone lymphomas being radiation therapy. On the other hand, few clinicians would treat multifocal PBL with just radiation, but rather combination therapy vs. chemotherapy depending of field of radiation. With that said, it would important to discuss how classifying mPBL with SBL will change these patients' management. Aside from providing prognostic relevance, it is hard to extrapolate treatment relevance from this study since one would treat multifocal disease more aggressively than unifocal disease anyway.

Response:
Thank you for your advice. It is exactly as you said that aside from providing prognostic relevance, it is difficult to extrapolate treatment relevance from this study. We have summarized the treatments in the patients with DLBCL in the revised manuscript, and we recognized that our patients with mPBL were indeed treated in a similar manner to SBL, which further supported the rationale for diagnosing “mPBL” as SBL. (Pg 10 and table 4; Pg 15, lines 15-17)

Typos such as SLB for SBL, male female ratio with slightly male predominance of “1:5” etc.

Response:
The errors have been corrected.

Tables:
1. What is the rationale for calling the 8 patients with unifocal PBL and node involvement as PBL? Also the staging details of the unifocal PBL is unclear? How do you reconcile Stage 1, II and IVE within unifocal PBL? Page 8 lines 7-12 are not
clear either and something is not right there. In addition, there is an overwhelming white predominance across all groups. Is this reflective of the disease characteristic or is it reflective of the geographic racial subgroups within the area?

Response:
As we mentioned in the Background section, the 2013 World Health Organization (WHO) classification for bone/soft tissue tumors defined PBL as a neoplasm composed of malignant lymphoid cells, producing one or more masses within bone, without any supra-regional lymph-node involvement or other extra-nodal lesions. According to the new WHO classification, patients with a single bone lesion and regional lymph node involvement are also considered as PBL, and are classified as stage IIE (as described below).

We have described the staging details of the unifocal PBL in our previous study as follow: “Unifocal localized bone lesions were classified as stage IE, whereas a single bone lesion with regional lymph node involvement and/or adjacent soft tissue extension was classified as stage IIE. Cases with either multifocal bone involvement or bone marrow involvement were considered as stage IV. Stage III was not included in our study because all cases with distant nodal involvement were not considered as PBL.” Based on your suggestion, we have inserted a statement that “Patients were staged retrospectively according to the Ann Arbor staging system as described before” and cited our previous study in the Methods section. (Pg 7, lines 13-14)

As for the ethnic background, there was white predominance in our groups. However, we don’t think we could make any conclusions only based on our single institutional experience.

2. Table 2 is very busy and not informative.
Response:
Table 2 and related information in the manuscript has been trimmed to be more concise.

3. There are 4 cases called ‘not-further subclassified’. Were these lymphomas-B vs T-vs null, based on what stains? Also, cases of splenic lymphomas with marrow involvement also need to be discussed, if present.
Response:
We have provided additional information in the table footnotes. ‘Not-further subclassified’ stands for ‘low-grade B-cell lymphoma no further information for subclassification’ in our manuscript. (pg 22, table 1)

4. IHC details is also not very clearly depicted. Mum1 was not done in most cases but then many were BCL-2+. It would be good to know the proliferation and maybe the MYC IHC status is available since majority of cases classified as PBL are DLBCLs. It would better for the table to be depicted as a bar graph or at the least depicted as likely GC-origin vs. non-GC origin and give numbers of BCL2+ cases within these
two subgroups.

Response:
Please see the similar above question and reply on page 4 in the response letter.

4. At least, a comparison of the T-cell with the historic control of systemic stage IV T-cell lymphomas would be more appropriate. Again the control would have to be age and LDH adjusted for both the groups. The survival curves should include the n in each group. So is the comparison of non-T cell vs T cell include all 4 groupings (the two SBL, uPBL, mPBL). This does not make sense.

Response:
Given the rarity of T-cell histology and histological heterogeneity in our series, T cell lymphoma has been removed from the prognostic factor analyses according to your suggestion.
Reviewer 2

Reviewer: Brad Haverkos
Reviewee's report:

Major:
- A brief sentence or two on the new 2013 WHO criteria would be helpful to the reader. In doing so I would very clearly state how you defined “PBL” and “SBL.” The definitions of uPBL, mPBL, initial SBL, recurrent SBL are clear but further defining the differences between SBL and PBL for your paper is essential. For example, it is unclear how you labeled someone as mPBL with LN involvement rather than this person having SBL.

Response:
We agreed your points. Here we have to clarify that mPBL with regional lymph node involvement should be taken as primary bone origin while mPBL with supraregional LN involvement has been considered SBL according to 2013 WHO criteria. The concept will be reflected throughout the whole text.

In the Introduction section we described the concept accordantly: “Recently, the 2013 World Health Organization (WHO) classification for bone/soft tissue tumors defined PBL as a neoplasm composed of malignant lymphoid cells, producing one or more masses within bone, without any supra-regional lymph-node involvement or other extra-nodal lesions.” (Pg 4, lines 20-22; Pg 5, lines 1) According to the criteria, multiple bone lesions with regional lymph node involvement and without other extra-nodal lesions are also classified as PBL. Therefore, we labeled these cases as mPBL with LN involvement rather than this person having SBL. To clearly state how we defined “PBL” and “SBL”, we have also stated “According to the criteria, bone lymphoma with/without regional lymph node and without other extra-nodal lesions was also classified as PBL.” in the Introduction section. (Pg 5, lines 1-4)

- A description of why you chose to stratify PBL between uPBL/mPBL and SBL into initial SBL/recurrent SBL would be important to include in the intro. Separating into these variables does not align with your objectives of describing differences between SBL and PBL. I agree they represent different entities, but I would alter the aims to reflect the rationale or alter the analysis to reflect your current aims of SBL v. PBL. At a minimum, I would explain your hypotheses on how/why you expected these groups to be different. Otherwise it just seems like you didn’t see a difference between PBL and SBL and so you decided post-hoc to separate out the groups to get statistical difference.

Response:
We chose to stratify PBL into uPBL/mPBL because we aimed to explore the prognostic role of multifocality in PBL. We have made a description in the “Introduction section”. (Pg 5, lines 8-10) Given that patients with recurrent lymphoma would have a worse prognosis, we had stratified SBL into initial SBL/recurrent SBL. However, given the relatively small sample sizes of both SBL
groups, they have been combined into one group in the revised manuscript.

- Pg 7 lines 7-8: Having searched SSDI, it is quite possible that people die and cannot be located in the index. Under your parameters these patients would still be listed as living and censored after July 1, 2013. I think it would be more fair to censor from last follow-up unless they have a death date in SSDI.

Response:
Thank you for your helpful advice. We have made revision according to your suggestion. We have stated “OS was calculated from the date of diagnosis to the date of death from any cause using the Social Security Death Index (SSDI). For unknown deaths, patients were censored at last follow-up” in the Methods section. (Pg 8, lines 2-4; Pg 11; table 5 and 6; figure 1)

- It seems like a stretch to make any conclusion on T cell histology outcomes when so few pts had TCL. I would remove these statements about T-cell histology outcomes given small #s.

Response:
Given the histological heterogeneity and the relatively rarity of the other histological subgroups, only patients with diffuse large B-cell lymphoma (DLBCL) were further reviewed for patient characteristics and analyzed for prognostic factors in our revised manuscript. (Pg 6, lines 18-20) T-cell lymphoma and classical Hodgkin lymphoma have been excluded from the univariate and multivariate analysis and these statements about T-cell histology outcomes have also been deleted in the revised version.

- There is no mention of treatment. I think this would be essential to add since your main conclusions are related to outcome. I assume you have this information. If not, I would state the rationale for not including this information.

Response:
According to your suggestion, the treatment has been described and discussed in the revised manuscript. (Treatment: Pg 10 and table 4; Pg 15, lines 15-17). Given the histological heterogeneity and the small sample size of other histological subgroups, only the treatment of DLBCL patients were summarized.

- It appears there were no differences between non-DLBCL vs. DLBCL. I do find this hard to believe, but if this is true I think this as important as any other finding in the paper and needs to be highlighted. I would emphasize this point and more clearly separate out indolent vs. aggressive subtypes and see if there is a difference in outcome. More discussion on lymphoma subtype and treatment in relation to outcome is warranted.

Response:
As you mentioned, there were no differences between non-DLBCL vs. DLBCL in our study, which should mainly attributed to the great histological heterogeneity of bone
lymphoma in our study. Given the great histological heterogeneity, only patients with DLBCL were further analyzed for prognostic factors in our revised manuscript, and thus we were unable to compare the difference in outcome between indolent and aggressive subtypes. It would be a great propose for our further study when we have collected more cases with complete clinical follow up or for multicenter efforts in the near future. The relationship between treatment and outcome in PBL has been discussed in our previous study (Wu H, et al. British journal of haematology 2014, 166(1):60-68), and thus it will not be discussed in our current study to avoid redundant information

**Minor:**
- Sentence on line 22 pg 4 to line 1 pg 5 needs grammar corrected.
  **Response:**
  It has been corrected to “However, limited information was available for the prognostic value of multifocality in PBL.” (Pg 5, line 8)

- Table 1: should be SBL rather than SLB
  **Response:**
  It has been corrected.

- On several occasions you say SLB rather than SBL (pg 8). Please stay consistent
  **Response:**
  It has been corrected.

- Pg 12, lines 11-14: This is not clear. What is the main point? Proportions do not change based on the # of cases.
  **Response:**
  What we meant was that compared with PBL groups, SBL group had a higher proportion of cHL and thus a relatively lower proportion of DLBCL. The uPBL group had a significantly higher proportion of DLBCL (80.4%, 37 of 46 cases) than the SBL group (50.0%, 23 of 46 cases), mainly due to fewer classical Hodgkin lymphoma and follicular lymphoma cases in the uPBL group. (Pg 14, lines 1-5; Pg 17, lines 14-17)

- Pg 13, line 13: BL is highlight associated with EBV only in endemic variant. I do not think I would include any of the discussion about EBV other than saying that all the DLBCL was EBER negative.
  **Response:**
  We have significantly trimmed the discussion according to your critique. Since incomplete EBV data available for both SBL and PBL, no further discussion is conducted in the study.

**Discretionary:**
- Pg 13, line 9-11: It seems obvious that patients with recurrent bone involvement would have worse prognosis (ie. Patients with relapsed disease do worse)
Response:
As you mentioned, it seems obvious that patients with recurrent bone involvement would have a worse prognosis, which is also the reason for us to stratify our SBL patients into two groups: initial SBL and recurrent SBL. However, although SBL with recurrent bone involvement showed a trend towards the worst prognosis among the mPBL and SBL groups in our study, the results did not reach statistical significance compared to either the mPBL group or the initial SBL group, probably due to the limited sample size of these groups. Given the relatively small sample sizes of both SBL groups, they have been combined into one group in the revised manuscript.

- Pg 11, line 13: I would not call SBL a “control group”
Response:
Thank you for your valuable advice. The terminology has been stopped use in the revised version, “compared group” is used to replace “control group” (Pg 13, line 8).

- I would elaborate in the discussion more on the characterization of PBL with locoregional LN involvement as PBL. In general, it is not clear in these cases if this is extra nodal extension of LN into bone or vice versa.
Response:
In most cases with locoregional LN involvement in our PBL series, the LNs are the draining lymph node near the bone disease, and thus were considered as locoregional LN involvement by PBL. As you mentioned, it is difficult to clearly delineate the primary site in bulky lesions with extensive involvement of bone and adjacent lymph nodes/soft tissue. In our study, when the lesion/lymphoma was mainly located at lymph nodes/soft tissue with only limited extension to bone, plus general lymphadenopathy, it should be classified as SBL rather than PBL.

- In line 1-2 page 6, does this mean iliac bone marrow involvement by imaging or by bone marrow biopsy? Please clarify. I assume this is radiographic involvement and then followed by a CT guided biopsy? If that is the case I think this sentence should be removed as it adds more confusion. If these are patients that had a random bone marrow biopsy and were identified to have lymphoma, I question the validity of including these patients as they most likely would have other sites involved and couldn’t be considered PBL. If these patients are all SBL patients with involvement on bone marrow biopsy I would state that clearly.
Response:
Bone marrow involvement is confirmed by routine staging bone marrow biopsy from iliac crest per NCCN guideline. If bone lymphoma involving isolateral posterior iliac crest, bone marrow biopsy was performed on the opposite iliac crest as routine to help clinical staging. For those patients who were initially diagnosed lymphoma by iliac
bone marrow biopsy, a further systemic investigation is necessary to rule out SBL. As described in our previous study (Wu H, et al. British Journal of Haematology 2014, 166(1):60-68), the current definition of PBL still remains somewhat controversial.


To make our point more clear, we have stated, “bone lymphoma with distant bone marrow involvement as the only other site of extranodal disease was also classified as PBL (stage IV) in our present study, because previous studies has demonstrated that it has a similar prognosis to that with localized disease. (Pg 6, lines 15-20)

- If allowable per the editor a key with definitions of PBL, uPBL, mPBL, SBL

Response:

PBL: Bone lymphoma with/without regional lymph node involvement and without other extra-nodal lesions are classified as PBL, regardless of whether the bone lesion was unifocal or multifocal. Bone lymphoma with distant bone marrow involvement as the only other site of extranodal disease was classified as stage IV PBL.

uPBL: PBL with single bone lesions

mPBL: PBL with multiple bone lesions

SBL: Bone lymphoma that can’t be classified as PBL (Bone lymphoma with supra-regional lymph-node involvement and/or other extra-nodal lesions).

The definitions of PBL, uPBL and mPBL have been included in the “Introduction” section, which allow reader easily to follow. (PBL: Pg 5, lines 1-4; uPBL and mPBL: Pg 5, lines 13-14) All other bone lymphoma should be classified as SBL.
Editor's comment:
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I'm willing to consider acceptance of this article providing major changes and revisions are being done to this manuscript in accordance to the reviewer's suggestions.
- The authors include several groups of B-cell lymphomas, low grade and high grade, Hodkin lymphoma and event T-cell lymphomas. This seems to be a very heterogeneous group of diseases with very different treatment regimens and outcomes. It will be much better to analyze the group of DLBL and DLBCLU for prognosis, rather than including a whole set of different entities.

Response:
We have taken your suggestion and reconstruct the manuscript to keep more homogeneity of disease groups for comparison. Only those patients with DLBCL were analyzed for prognostic factor analyses.

- More information regarding treatment and laboratory findings is needed.
Response:
Treatment regimens and LDH information has been included. (Treatment: Pg 10 and table 4; Pg 15, lines 15-17) (LDH: table 2 and 5 and Pg 11, lines 20-22)

- More information regarding MUM1, and FISH findings (e.g. MYC and IGH-BCL-2) is needed
Response:
Please see the similar above question and reply on page 4 in the response letter.

- I'd like to have an explanation of what does this manuscript add to their previous publication in BJH (Br J Haematol. 2014 Jul;166(1):60-8. doi: 10.1111/bjh.12841. Epub 2014 Mar 27. Prognostic significance of soft tissue extension, international prognostic index, and multifocality in primary bone lymphoma: a single institutional experience. Wu H1, Zhang L, Shao H, Sokol L, Sotomayor E, Letson D, Bui MM.) Why was this publication not mentioned among their references?
Response:
Please see the similar above question and reply on pages 2 and 3 in response letter. Our current manuscript was submitted to BMC Cancer on 1 April 2014, while our BJH paper was first published online on 27 March 2014 and formally published in Jul 2014. This is the reason why our BJH paper was not mentioned in our previous study since it was not officially published. The BJH paper has been cited and discussed by the current manuscript. (Pg 5, lines 4-7; Pg 7, lines 13-14)

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Editorial requests:
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1) Please include e-mail addresses of all authors on the title page.
Response:
E-mail addresses of all authors have been included on the title page.

2) Please include a conclusion section.

This should state clearly the main conclusions of the research and give a clear explanation of their importance and relevance. Summary illustrations may be included.

Response:
A conclusion section has been included according to your kind suggestion.